PATENT
Docket No. 219002028310

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Tami M. Procopio

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Babu J. MAVUNKEL, *et al.*

Serial No.: Not yet assigned
Divisional of 09/128,137

Filing Date: Herewith

For: COMPOUNDS AND METHODS TO TREAT CARDIAC FAILURE AND OTHER DISORDERS

Examiner: Not yet assigned,

Group Art Unit: Not yet assigned,

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

This application is filed in order to prosecute claims to subject matter that was not considered in the parent application. Prior to examination, please amend the specification and claims as follows:

sd-77130

AMENDMENT

In the Specification:

Please replace the first paragraph at lines 4-9 of page 1 with:

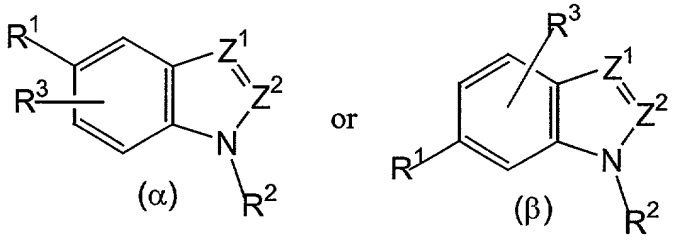
--This application is a divisional application of U.S. Application Serial No. 09/316,761 filed 21 May 1999, and now pending which is a continuation-in-part of U.S. Application Serial No. 09/275,176, filed 24 March 1999, now U.S. patent 6,340,685,, which is a continuation-in-part of U.S. Serial No. 09/128,137, filed 3 August 1998 and now U.S. patent 6,130,235, which application claims priority under 35 U.S.C. § 119(e) of provisional application 60/086,531 filed 22 May 1998. The contents of these applications are incorporated herein by reference.--

Please amend the claims as follows:

In the Claims:

Please cancel claims 1-38 and replace them with the following claims:

39. (New) A compound of the formula:



and the pharmaceutically acceptable salts thereof,

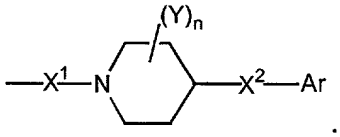
wherein each of Z^1 and Z^2 is independently CR^4 or N;

where each R^4 is independently selected from the group consisting of H, alkyl (1-6C) and aryl, each of said alkyl and aryl optionally including one or more heteroatoms selected from O, S, and N and each of said alkyl being optionally substituted by one or more substituents selected from the group consisting of halo, OR, SR, NR_2, RCO, COOR, $CONR_2$, OOCR, NROCR, CN, =O, a five- or six-membered saturated carbocyclic ring or heterocyclic ring containing 1-2 N, and a six-membered aromatic ring optionally containing 1-2 N, where R in the foregoing

optional substituents is H or alkyl (1-6C) and each of said aryl being optionally substituted by one or more substituents selected from the group consisting of halo, OR, SR, NR_2, RCO, COOR, $CONR_2$, OOCR, NROCR, CN, a five- or six-membered saturated carbocyclic ring or heterocyclic ring containing 1-2 N, and a six-membered aromatic ring optionally containing 1-2 N, where R in the foregoing optional substituents is H or alkyl (1-6C); or

two R^4 taken together form a bridge optionally containing a heteroatom;

R^1 is



;

wherein

X^1 is CO, or an isostere thereof;

Y is optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl or two Y taken together may form an alkylene (2-3C) bridge;

n is 0, 1 or 2;

X^2 is CH, CH_2 or an isostere thereof; and

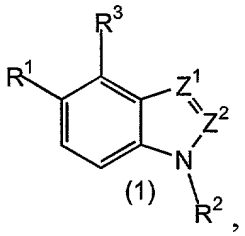
Ar consists of one or two phenyl moieties directly coupled to X^2, said one or two phenyl moieties being optionally substituted by one or more substituents selected from the group consisting of halo, nitro, alkyl (1-6C), alkenyl (1-6C), alkynyl (1-6C), CN, CF_3, RCO, COOR, $CONR_2$, NR_2, OR, SR, OOCR, NROCR; and phenyl, itself optionally substituted by one or more of the foregoing substituents, wherein R in the foregoing optional substituents is H or alkyl (1-6C);

R^2 is selected from the group consisting of H, alkyl (1-6C) and aryl, each of said alkyl optionally including one or more heteroatoms which are selected from O, S and N, and each of said aryl or alkyl being optionally substituted by one or more substituents selected from the group consisting of halo, OR, SR, NR_2, RCO, COOR, $CONR_2$, OOCR, NROCR, CN, =O, a five- or six-membered saturated carbocyclic ring or heterocyclic ring containing 1-2 N, and a six-membered aromatic ring optionally containing 1-2 N, where R in the foregoing optional substituents is H or alkyl (1-6C) and each of said aryl being optionally substituted by one or more substituents selected from the group consisting of halo, OR, SR, NR_2, RCO, COOR, $CONR_2$, OOCR, NROCR, CN, a five- or six-membered saturated carbocyclic ring or

heterocyclic ring containing 1-2 N, and a six-membered aromatic ring optionally containing 1-2 N, where R in the foregoing optional substituents is H or alkyl (1-6C);

R^3 is selected from the group consisting of H, halo, NO_2, alkyl (1-6C), alkenyl (1-6C), alkynyl (1-6C), CN, OR, SR, NR_2, RCO, COOR, $CONR_2$, OOCR, and NROCR where R is H or alkyl (1-6C).

40. (New) The compound of claim 39 which is of the formula



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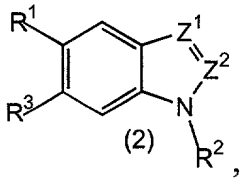

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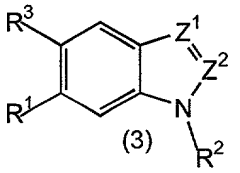
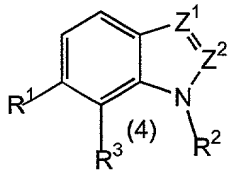


or



41. (New) The compound of claim 39 wherein R^2 is alkyl (1-6C) or aryl, each of said alkyl or aryl optionally including one or more heteroatoms which are selected from O, S and N, and each of said alkyl being optionally substituted by one or more substituents selected from the group consisting of halo, OR, SR, NR_2, RCO, COOR, $CONR_2$, OOCR, NROCR, CN, =O, a five- or six-membered saturated carbocyclic ring or heterocyclic ring containing 1-2 N, and a six-membered aromatic ring optionally containing 1-2 N, where R in the foregoing optional substituents is H or alkyl (1-6C) and each of said aryl being optionally substituted by one or more substituents selected from the group consisting of halo, OR, SR, NR_2, RCO, COOR, $CONR_2$, OOCR, NROCR, CN, a five- or six-membered saturated carbocyclic ring or heterocyclic ring containing 1-2 N, and a six-membered aromatic ring optionally containing 1-2 N, where R in the foregoing optional substituents is H or alkyl (1-6C).

42. (New) The compound of claim 39 wherein X^1 is CO.

43. (New) The compound of claim 39 wherein X^2 is CH_2.

44. (New) The compound of claim 39 wherein X^1 is CO and X^2 is CH_2.

45. (New) The compound of claim 39 wherein Z^1 and Z^2 are CR^4.

46. (New) The compound of claim 44 wherein Z^1 and Z^2 are CR^4.

47. (New) The compound of claim 39 wherein Z^1 is N and Z^2 is CH.

48. (New) The compound of claim 44 wherein Z^1 is N and Z^2 is CH.

49. (New) The compound of claim 40 which is of the formula (2).

50. (New) The compound of claim 44 which is of the formula (2).

51. (New) The compound of claim 40 wherein R^3 is halo or OR where R is alkyl (1-6C).

52. (New) The compound of claim 44 wherein R^3 is halo or OR where R is alkyl (1-6C).

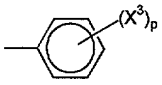
53. (New) The compound of claim 44 wherein R^2 is alkyl (1-6C) or is aryl, each of said alkyl or aryl constituting the substituent R^2 optionally including one or more heteroatoms which are selected from O, S and N, and each said alkyl optionally substituted by one or more substituents selected from the group consisting of halo, OR, SR, NR_2, RCO, COOR, $CONR_2$, OOCR, NROCR (where R is H or 1-6C alkyl), CN, =O, a five- or six-membered saturated carbocyclic ring or heterocyclic ring containing 1-2 N, and a six-membered aromatic ring optionally containing 1-2 N and each of said aryl being optionally substituted by one or more substituents selected from the group consisting of halo, OR, SR, NR_2, RCO, COOR, $CONR_2$, OOCR, NROCR, CN, a five- or six-membered saturated carbocyclic ring or heterocyclic ring containing 1-2 N, and a six-membered aromatic ring optionally containing 1-2 N, where R in the foregoing optional substituents is H or alkyl (1-6C).

54. (New) The compound of claim 39 wherein n is 1 or 2 and Y is unsubstituted alkyl.

55. (New) The compound of claim 52 wherein Z^3 is 1 or 2 and Y is unsubstituted alkyl.

56. (New) The compound of claim 39 wherein n is 0.

57. (New) The compound of claim 52 wherein n is 0.

58. (New) The compound of claim 39 wherein Ar is  wherein each X^3 is independently alkyl (1-6C), halo, OR, or NR_2 and p is 0, 1, 2 or 3.

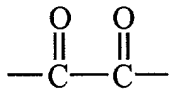
59. (New) The compound of claim 39 wherein Z^2 is CH and wherein R^2 is alkyl (1-6C) or is aryl, each of said alkyl or aryl constituting the substituent R^2 optionally including one or more heteroatoms which are selected from O, S and N, and each said alkyl optionally substituted by one or more substituents selected from the group consisting of halo, OR, SR, NR_2, RCO, COOR, $CONR_2$, OOCR, NROCR (where R is H or 1-6C alkyl), CN, =O, a five- or six-membered saturated carbocyclic ring or heterocyclic ring containing 1-2 N, and a six-membered aromatic ring optionally containing 1-2 N and each of said aryl being optionally substituted by one or more substituents selected from the group consisting of halo, OR, SR, NR_2, RCO, COOR, $CONR_2$, OOCR, NROCR, CN, a five- or six-membered saturated carbocyclic ring or heterocyclic ring containing 1-2 N, and a six-membered aromatic ring optionally containing 1-2 N, where R in the foregoing optional substituents is H or alkyl (1-6C).

60. (New) The compound of claim 39 wherein Z^1 is CR^4 and R^4 is other than H.

61. (New) The compound of claim 39 wherein Z^1 is CR^4 wherein R^4 is other than H and Z^2 is CH.

62. (New) The compound of claim 61 wherein R^4 is alkyl either containing one or more heteroatoms selected from O, S and N, or said alkyl being substituted by one or more substituents selected from the group consisting of halo, OR, SR, NR_2, RCO, COOR, $CONR_2$, OOCR, NROCR, CN, =O, a five- or six-membered saturated carbocyclic ring or heterocyclic ring containing 1-2 N, and a six-membered aromatic ring optionally containing 1-2 N, where R in the foregoing optional substituents is H or alkyl (1-6C); or both.

63. (New) The compound of claim 62 wherein R^4 comprises the structure



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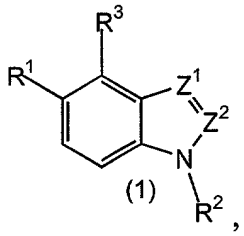
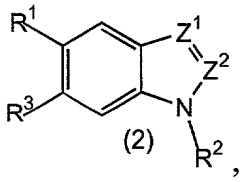
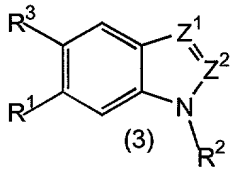
64. (New) The compound of claim 63 which is of the formula



(1),

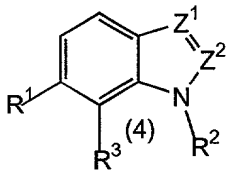


(2),



(3)

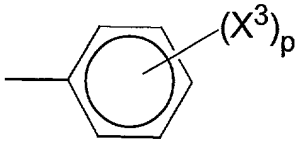
or



(4)

65. (New) The compound of claim 64 which is of the formula (2).

66. (New) The compound of claim 62 wherein Ar is



wherein each X^3 is independently alkyl (1-6C), halo, OR; or NR_2 and p is 0, 1, 2 or 3.

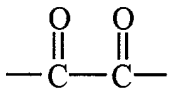
67. (New) The compound of claim 62 wherein R^3 is halo or OR where R is alkyl (1-6C).

68. (New) The compound of claim 62 wherein R^4 comprises NR_2.

69. (New) The compound of claim 62 wherein R^4 comprises a saturated 5 or 6 membered ring containing 1-2 heteroatoms.

70. (New) The compound of claim 62 wherein R^4 comprises an unsaturated 5 or 6 membered ring containing 1-2 heteroatoms.

71. (New) The compound of claim 66 wherein R^4 comprises the structure:



72. (New) The compound of claim 39 which is selected from the group consisting of:

4-benzylpiperdinyl indole-5-carboxamide;

4-chloro-4-benzylpiperidinyl indole-5-carboxamide;

6-chloro-4-benzylpiperidinyl indole-5-carboxamide;

4-chloro-(4-(4-fluorobenzyl) piperidinyl)-indole-5-carboxamide;

6-chloro-(4-(4-fluorobenzyl) piperidinyl)-indole carboxamide;

4-methoxy-(4-benzylpiperidinyl)-indole-5-carboxamide;

6-methoxy-(4-benzylpiperidinyl)-indole-5-carboxamide;

4-methoxy-(4-(4-fluorobenzyl) piperidinyl)-indole-5-carboxamide;

6-methoxy-(4-(4fluorobenzyl) piperidinyl)-indole-5-carboxamide;

N-(3-cyclohexylmethylamino-2-hydroxypropyl)-(4-benzylpiperidinyl)-indole-5-carboxamide;

N-(3-N-methylpiperazinyl-2-hydroxypropyl)-(4-benzylpiperidinyl)-indole-5-carboxamide;

N-(3-benzylamino-2-hydroxypropyl)-(4-benzylpiperidinyl)-indole-5-carboxamide;

N-[3-{(4-methoxybenzyl)-amino}-2-hydroxypropyl-]-(4-benzylpiperidinyl)-indole-5-carboxamide;

N-{3-n-propylamino-2-hydroxypropyl}-(4-benzylpiperidinyl)-indole-5-carboxamide;

N-(4-pyridoyl)-(4-benzylpiperidinyl)indole-5-carboxamide;

N-(4-pyridylmethyl)-(4-benzylpiperidinyl)-indole-5-carboxamide;

N-methylacetyl-(4-benzylpiperidinyl)-indole-5-carboxamide;

N-acetyl-4-benzylpiperidinyl indole-5-carboxamide;

N-(n-propylamide)acetyl 4-benzylpiperidinyl indole-5-carboxamide;

4-benzylpiperidinyl-indole-5-carboxamide-1-acetic acid-n-butylamide;

4-benzylpiperidinyl-indole-5-carboxamide-1-acetic acid 4-methoxybenzyl amide;

3-(2-methoxyethylaminocarboxamidyl)-(4-benzylpiperidinyl)indole-5-carboxamide;

3-(2-methylaminoethylaminocarboxamidyl)-(4-benzylpiperidinyl)indole-5-carboxamide;

3-(2-aminoethylaminocarboxamidyl)-(4-benzylpiperidinyl)indole-5-carboxamide;

3-(4-benzylpiperidinylcarboxamidyl)-(4-benzylpiperidinyl)indole-5-carboxamide;

3-(4-benzylpiperidinylcarboxamidyl)-(4-benzylpiperidinyl)indole-6-carboxamide;

3-(4-fluorobenzylcarboxamidyl)-(4-benzylpiperidinyl)indole-5-carboxamide;

3-[2-(3,5-dimethoxyphenyl)ethylcarboxamidyl]-(4-benzylpiperidinyl)indole-5-carboxamide;

6-methoxy-(4-benzylpiperidinyl)indole-5-carboxamide;

3-trifluoroacetyl-(4-benzylpiperidinyl)indole-5-carboxamide;

6-methoxy-3-(2-dimethylaminoethylamino)carboxamidyl-(4-benzylpiperidinyl)indole-5-carboxamide;

3-trifluoroacetyl-4-benzylpiperidinylindole-5-carboxamide;

4-benzylpiperidinyl indole-5-carboxamide-3-carboxylic acid;

3-(2-dimethylamino)ethylaminocarboxamidyl-(4-benzylpiperidinyl)indole-5-carboxamide;

or is a compound as set forth in Table 5.

73. (New) The compound of claim 72 which is

4-benzylpiperdinyl indole-5-carboxamide;

3-[2-dimethylaminoethylaminocarbonyl]-4-benzylpiperidinyl-6-methoxy indole-5-carboxamide; or

4-benzylpiperidinyl-6-methoxy benzimidazole-5-carboxamide.

74. (New) The compound of claim 73 which is 4-benzylpiperdinyl indole-5-carboxamide

75. (New) A method to treat a condition characterized by a pro-inflammation response which method comprises administering to a subject in need of such treatment an amount of a compound of claim 39 or a pharmaceutical composition thereof effective to treat said condition.

76. (New) The method of claim 75 wherein said condition characterized by inflammation is acute respiratory distress syndrome, asthma, chronic obstructive pulmonary disease, uveitis, IBD, acute renal failure, head trauma, or ischemic/reperfusion injury.

77. (New) A method to treat a heart condition associated with cardiac failure, which method comprises administering to a subject in need of such treatment an amount of a compound of any of claim 76 or a pharmaceutical composition thereof effective to treat said heart condition.

78. (New) The method of claim 77 wherein said chronic heart condition is congestive heart failure, cardiomyopathy or myocarditis.

REMARKS

The proposed claims are limited to embodiments which were withdrawn from consideration in the parent application. The present claims represent embodiments of the generic formula set forth in the parent wherein Z^3 is CH and m is 1 - *i.e.*, piperidinyl compounds. These were classified in Group I in the parent; Group II had been elected wherein Z^3 was N and m =1 - *i.e.*, the piperazinyl compounds. U.S. patent 6,130,235 which contains claims to compounds comprising piperidine was issued on the great-grandparent application.

The claim wording has also been modified to take account of suggestions and amendments made for clarity in the parent application. No new matter has been added and entry of the amendment is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 219002028310.

Respectfully submitted,

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